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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/645,546	08/22/2003	Bruce K. Krueger	028754-042	9617

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HC

Office Action Summary	Application No.	Applicant(s)	
	10/645,546	KRUEGER ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8,13-18,21-23,27-28 and 33-46* is/are pending in the application.

4a) Of the above claim(s) *5-8,21-23,27,28 and 33-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1-4-05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 19, 2005 has been entered. Pending claims are 1-3, 7, 8, 13-18, 21-23, 27, 28 and 33-46.

Applicant's election with traverse of Group I in the reply filed January 19, 2005 is acknowledged. The traversal is on the ground(s) that Groups I-XV are classified the same class and subclass. This is not found persuasive because although the groups are classified in the same class and subclass the nucleic acids being administered or contacted to hippocampal cells are materially different and separate. However, the subject matter of groups II-XV have materially different effects from the effect obtain from the method of group I. In group I, the contacting would increase intrahippocampal levels of TrkB, or TrkB isoforms to treat a neurodegenerative disorder. Group II, to methods of contacting that would increase intrahippocampal levels of TrkB, or TrkB isoforms to prevent a neurodegenerative disorder. The treatment of a neurodegenerative disorder requires materially different methods compared to preventing a neurodegenerative disorder. Group III, to methods of contacting hippocampal neurons with a nucleic acid encoding antisense TrkB mRNA, are materially different and separate from group I as antisense mRNA would hybridize to TrkB mRNA/gene and inhibit either production of TrkB or inhibit expression of TrkB gene. The result would be a decrease in TrkB. Thus, the restriction of claims 7 and 8 is maintained because they are of separate effect. With regard to groups VI-X, and XII-XIII, TrkC is a distinct tyrosine receptor kinase from TrkB. Methods of contacting hippocampal neurons with a nucleic acid encoding either TrkC or antisense to TrkC mRNA would not result in an increase in TrkB as required for group I. Thus, groups III-XV are also independent because of separate

effects. There is no requirement for groups to be classified separately when independence can be shown.

The requirement is still deemed proper and is therefore made FINAL.

Further claims 13-16 and 18 are examined only with regards to the subject matter of group I. Claims 1-3, 13-16 and 18 are examined in this office action. Claims 4-12, 17, and 21-23, 27, 28 and 33-46 are withdrawn from consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 13-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of contacting hippocampal neurons under *in vitro* conditions with an amount of isolated nucleic acid encoding full-length TrkB or any mutant, variant, homolog, or fragment thereof having the same activity as said full-length TrkB, does not reasonably provide enablement for a method of contacting hippocampal neurons under *in vivo* conditions with an amount of isolated nucleic acid encoding full-length TrkB or any mutant, variant, homolog, or fragment thereof having the same activity as said full-length TrkB. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-3, 13-16 and 18 are drawn to methods where the result in increasing the amount of TrkB in treated hippocampal neurons over nontreated hippocampal neurons.

However, when the claims are read in light of the specification, the only use for in vivo contacting is for the treatment of neurodegenerative diseases.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The claimed method is to contacting hippocampal neurons with an amount of isolated nucleic acid encoding full-length TrkB or any mutant, homolog, variant, or fragment thereof having the same activity of full-length TrkB. The claimed invention is not enabled because the specification as filed fails to provide sufficient guidance for how to make and use the claimed method and an artisan of skill would require undue experimentation to make and use the method as recited because the art of treating a

neurodegenerative disorder was unpredictable at the time of filing and is unpredictable even today as discussed below.

The methods of claims 1-3, 13-16 and 18 are to contacting hippocampal neurons with an amount of isolated nucleic acid encoding full-length TrkB or any mutant, homolog, variant, or fragment thereof having the same activity of full-length TrkB. Wherein contacting hippocampal neurons with an isolated nucleic acid encoding full-length TrkB or any mutant, homolog, variant, or fragment thereof is sufficient to increase the amount of full-length TrkB in hippocampal neurons compared to untreated neurons. The claims, however, when read in light of the specification, are interpreted as being directed to gene therapy of neurodegenerative diseases (pg. 21 lines 17-19). As indicated in the scope of enablement, the specification provides only guidance for the *in vitro* delivery of TrkB to neurons, which are normal, non-diseased rat neurons. The specification fails to provide sufficient teachings or guidance to enable the skilled artisan to provide a gene therapy using the claimed methods. As will be discussed below, the specification does not provide those teachings for *in vivo* delivery to achieve a therapeutic effect that were not present in the art at the time of filing.

One skilled in the art at the time of filing would know that unpredictability occurs with regards to gene therapy treatments regardless of gene therapy vehicle. In this regard, the specification discloses that adenoviruses, retroviruses, herpesvirus, liposomes and polylysine conjugates can be used to deliver a nucleic acid encoding TrkB to neurons *in vivo* (page 21, lines 14-17). Unpredictability in the art with regards to the use of adenoviruses in gene therapy and target cells is exemplified by Peltekian et al. (1997, Journal of Neuroscience Methods, 71:77-84). Peltekian et al. teach the unpredictability of

gene therapy, specifically involving the treatment of disorders involving neurodegeneration (pg. 82, col. 1 parag. 3 lines 1-9). Peltekian et al. continue to teach that one of the central problems with gene therapy is the use of adenoviral vectors and targeting of specific cell types to elicit a therapeutic response (pg. 78 col. 1 parag. 3 bridge col. 2 parag. 1). Peltekian continues that brain physiology inherently diminishes integration and expression of viral vectors for gene therapy to reach cells of interest i.e. hippocampal neurons by at least two systems in the brain, the astrocytic glia limitans and the bundles of myelinated fibers surrounding neurons distributed throughout the brain which lead to diminished transfection of target cells. (pg. 79 col. 1 parag. 4). Peltekian continues that intraparenchymal injection in the hippocampus have additionally demonstrated that adenovirus vectors do no cross large fiber bundles of myelinated cells i.e. hippocampal neurons (pg. 79 col. 1 parag. 4 lines 15-19). Peltekian continues that transduction of neuronal cells continues to be a significant impediment to long-lasting treatment resulting from the fact that most neural cells are non-replicative, thus only a transitory expression of transgene occurs (pg. 79 col. 2 parag. 3), and "that adenovirus vectors can be toxic for neural cells" (pg. 80 col. 1 parag. 2 last sentence). Further support in the art for the unpredictability of non-viral and viral based vectors in gene therapy are exemplified by Somia et al. Somia teaches that naked DNA and liposomes, though produced in large amounts, suffer from inefficient gene transfer, and given the need of sustained and often high-level expression of the transgene for many diseases are not suitable since expression is only transient (pg. 91 col. 1 parag. 2 lines 1-10). Somia continues that with regard to retroviral vectors in gene therapy treatments, a main limitation "has been their inability to infect non-dividing cells, meaning that tissues such

as the brain, eye, lungs and pancreas are not amenable to direct *in vivo* gene delivery" (pg. 92 col. 2 parag. 3). With regard to gene therapy and all viral vectors Somia teaches that the biggest challenge facing viral based administration of a transgene is the immune response of the host (pg. 94 col. 2 parag. 5 lines 1-3). The host immune response to viral based gene therapy involves both a cellular response and a humoral response, that together significantly diminishes expression and continued administration of viral vectors (pg. 94 col. 2 last sentence bridge pg. 95 1st full parag.). Further teachings by Kennedy with regard to herpes based viral vectors (HSV) in gene therapy treatments of neurological disorders teach the following problems: 1) with "HSV-1 vectors there is the possibility that the virus may be inadvertently targeted to unintended and inappropriate sites", 2) "it is not known how the host-tissue promoters will interact/interfere with the function of promoter and enhancer elements in the vector", and 3) "it is not known whether resident latent HSV-1 in the target neurons will prevent the HSV-1 vector itself from establishing the required latent infection in those same neurons" (pg. 1253 col. 2 parag. 4). Therefore, based on the teachings of Peltekian, Somia and Kennedy, it is apparent that at the time of filing, the *in vivo* delivery of a nucleic acid encoding TrkB to hippocampal neurons to affect a particular disease symptom would have been regarded as lacking enablement.

Furthermore, the skilled artisan at the time of filing, would not have found the necessary guidance in the specification to provide enablement for a method of *in vivo* delivery to hippocampal cells for the treatment of a neurodegenerative disease. While the specification does propose modes of nucleic acid delivery as noted above, the specification provides no further guidance than adenovirus as a model of delivering a

nucleic acid encoding TrkB to Ts16 hippocampal neurons *in vitro* (pg. 43 lines 14-20). Ts16 neurons are normal, and as such are not representative of any neurological disease. The specification does not discuss TrkB levels needed to be achieved in order to provide an effective treatment for any neurodegenerative disease, or that the levels achieved in the examples given in Fig. 3C-E would be effective to treat any particular disease. For the record, treatment is being used as the alleviation of a symptom associated with a neurological disease. There is no gene therapy use for the *in vivo* delivery of a nucleic acid encoding TrkB to hippocampal neurons absent an alleviation of a symptom. Thus, the disclosure of *in vitro* adenoviral delivery of a nucleic acid encoding TrkB to Ts16 neurons cannot be correlated to *in vivo* treatment of a neurological disorder. Examples show in Figures 3 A-E shows the transfection of rat hippocampal neurons in culture with an adenovirus comprising a nucleic acid encoding human TrkB to rat hippocampal operably linked to a cytomegalovirus promoter (pg. 35 lines 23-25). Expression of the nucleic acid causes the production of TrkB, and since the nucleic acid encodes full length TrkB, the ratio of full length to truncated TrkB is increased. However, the *in vitro* results are not regarded as enabling a method of gene therapy because an alleviation of any symptom associated with a neurodegenerative disease is not addressed. Given the teachings in the art at the time of filing that gene therapy targeting neuronal cells is unpredictable, the specific examples are not seen as providing enabling guidance to the skilled artisan.

Additionally, it is noted that the specification fails to make any correlation between a neurodegenerative disease and abnormal TrkB levels or abnormal TrkB. The specification discloses Alzheimer's disease, and Parkinson's disease but a correlation

between these diseases and TrkB is not found in the specification, nor is one found in the art at the time of filing.

Thus, the specification and the art at the time of filing fail to provide sufficient guidance to the skilled artisan to use the claimed methods to treat any particular neurodegenerative disease because the art regarded gene therapy targeting neurons as unpredictable due to delivery issues, the specification fails to provide guidance for treatment efficacy using the claimed methods and no diseases had been identified that would benefit from an increase of TrkB in hippocampal neurons. At the time of filing, the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to effectively provide a gene therapy for a neurodegenerative disease using the claimed methods to increase hippocampal levels of TrkB.

Claims 1-3, 14-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1-3, 14 and 18 are drawn to a method of contacting hippocampal neurons with an amount of isolated nucleic acid encoding full-length TrkB or any mutant, variant, homolog or fragment thereof having the same activity as full-length TrkB. The specification doesn't define what is meant by full-length activity. For example, TrkB is known to bind brain derived neurotropic factor (BDNF) and potentate neuronal development and plasticity, and is suggested to be involved in the regulation of postsynaptic AChR clustering at the neuromuscular

junction, and the development of glutamatergic synapses (Klau et al. pg. 327 col. 2 parags. 2-3). Further, the truncated form of TrkB is known to work in either a dominate-negative effect on full-length TrkB or can play a role in ligand presentation (pg. 327 col. 2 parag. 3 lines 4-7). However, there is no description of any mutant, variant, homolog, or fragment thereof of TrkB having the same activity as full-length TrkB. Given the multiple roles of TrkB one would not know what "same activity" refers to with regard to a mutant, variant, homolog or fragment thereof. Thus possession at the time filing is not evident.

While the specification discloses a nucleic acid sequence that encodes full length TrkB, the specification does not teach mutants, variants, homologs, or fragments thereof of TrkB having the same activity as full-length TrkB. Thus, the skilled artisan cannot envision the detailed chemical structure of these nucleic acids, and conception is not achieved until reduction to practice has occurred. One of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by not mutants, variants, homologs, or fragments thereof of TrkB having the same activity as full-length TrkB

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Thus, the case law supports a finding that the claim has written description for a nucleic acid encoding TrkB, but not mutants, variants, homologs, or fragments thereof of TrkB having the same activity as full-length TrkB. Therefore, only the TIMP3 gene encompassed by SEQ ID NO:1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that "to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention".

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-3, 13-16 and 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a method of contacting hippocampal neurons with an amount of an isolated nucleic acid encoding full-length TrkB or any mutant, variant, homolog, or fragment thereof having the same activity as said full-length TrkB, whereby said amount of said isolated nucleic acid is sufficient to increase the amount of full-length TrkB in

said neurons compared to untreated neurons.

It is unclear from the claim with regard to any mutant, variant, homolog, or fragment thereof having the same activity as full-length TrkB. This is confusing because it is not clear if applicant means an activity particular to TrkB or an activity that TrkB has in common with other proteins. For example, all kinases phosphorylate a substrate. If applicant intends that the "same activity" be particular to TrkB, then it is suggested that applicant amend the claims to state "having a full-length TrkB activity." As presently written, the metes and bounds of "same activity" are not clear so that the reader would know when they are infringing the claimed invention.

Claim Rejections - 35 USC § 102

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 13-16 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kryl et al (1999) Journal of Neuroscience 19(14): 5823-5833.

Kryl et al. teach hippocampal neurons transfected with cDNA comprising either full-length TrkB or the truncated T1 form of TrkB (pg. 5828 col. 1 parag. 2 bridge col. 2 bridge pg. 5829 col. 1 parag. 1 and fig. 5). Kryl et al. continue that transfected hippocampal neurons showed even distribution of full-length and truncated TrkB in all areas of the cell structure (pg. 5828 col. 2 last sentence bridge pg. 5829 first sentence).Therefore, Kryl et al. clearly anticipates the claimed invention.

Claim Objections

Claim 14 is objected to because of the following informalities: Claim 14 have been added to group I. However, claim 14 contains subject matter not part of the elected invention. Applicants elected Group I encompassing nucleic acid encoding full-length TrkB. Applicant is requested to amend claim 14 to delete non-elected subject matter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari, Ph.D whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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